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NUTRITION REVIEWS

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Errata

Vol. 7, No. 7, p. 204, col. 2, paragraph 3, last line: "100^{6}" *should read* "10^{-6}"

NUTRITION REVIEWS

VOL. 7 OCTOBER, 1949 No. 10

NUTRITION, GERIATRICS, AND THE PHYSICIAN

Today a man of 60 may be as young, vigorous, and vital as the average man of 40. On the other hand, he may present the common picture of the man of 80, old, weak, and miserable.

Whether a man is old or young at 60 depends much upon the diet, but far more upon his nutrition.

Diet is only one of the departments of nutrition. The other components of nutrition would include the following:

Digestion. Transformation of food in the digestive tract by digestive fluids into forms which can be absorbed. This depends upon provision of good digestive products, all under autonomic nervous system management, *unhurried* (i.e., no cathartics, no diarrhea), *serene* (i.e., no nervous spastic tightness), and *competent* (i.e., complete chemical and mechanical preparation for absorption through the walls of the gastrointestinal tract).

Absorption. Transmission of digested food through the walls of the stomach and intestine into the blood and lymph circulation. This requires vital, healthy, receptive digestive tract tissues.

Processing and Further Transformation. Food products in the blood are again processed, notably in the liver, into forms that can be transported to the tissues where each particular kind is needed, accepted, and utilized for function and structure. The processing of protein fractions (amino acids) into tissue albumins is thought to be especially a liver responsibility.

Utilization. Utilization of transported nutrients in the tissues of the muscles, nerves, brain, organs, and where they are used for many different life processes and purposes.

Meeting Excessive Demands. Fever, burns, and hemorrhage make excessive demands, and sick or damaged organs may rob the rest of the body of its proper nutritional quota. For example, "renal rickets" is a body calcium starvation accompanying a certain kind of kidney disorder. Fever and burns may rob the body of much of its proteins.

Excretion. This may be too slow, causing disturbance in body chemistry or too rapid, resulting in waste and tissue poverty.

These are the pillars of good nutrition. They support health, vigor, and a youthful longevity. Not one should be neglected in the care and management of life at any age. They should be routinely examined and tested.

Ninety-five per cent of the patients coming to physicians do so for repair, less than 5 per cent for upkeep and pre-trouble maintenance. Men do not run their lives as intelligently as corporations run their business. Industry knows the value of the examination of equipment before it breaks down, the people don't. Perhaps they will learn, if physicians teach the importance of a thorough all-around examination and full study of the whole man and his whole life.

This is a large story. We shall confine our attention to the important points of what a physician can do for a man of 60 who comes for a thorough examination, prevention of trouble, build up of reserves of powers, and extension and enrichment of life.

The most common nutritional deficiencies at 60 are calcium, iron, proteins, vitamins of the B-complex, and vitamin A. Much malnutrition is due to lack of teeth, to sensitive teeth, dietary fads and prejudices, and poor "taste habits." Some old people would live on tea and toast, but not for long. Those without teeth and with tender gums cannot or will not eat meat, others will eat an excess of calories, become overweight, and die sooner. Some believe that animal proteins are evil and lose their biologic values.

The first thing to do in a nutrition survey is to find out what the patient really does eat. His verbal reports are frequently valueless. The nearest approximation to an exact record of kind and quantity of food eaten that a practicing physician can obtain from a patient is a report which is filled out hour by hour by the patient for four days, and which should include a weekend. This report can be studied and summarized for deficiencies and excesses. These are the first and most fundamental data of the nutrition survey. The four day diet record gives an account of what the patient reports that he has eaten. It is a report upon a basic element in the patient's life, the way he lives his four days. It is part of a life survey and an important part.

The next series of data to be obtained concern gastrointestinal motility and kidney speed and urinary clearance. Following the evening meal the patient is given three 15 grain capsules of carmine. The stools should be watched to see the first presence and the last presence of the red color. The ordinary standard is appearance in twelve hours and disappearance in thirty-six hours. Despite a daily bowel movement, 5 to 10 per cent of the patients are likely to have carmine present in the stools for six, seven, and ten days. At the same time 2 grains of methylene blue are given, with instructions to note and record the appearance of blue, followed by green, and then the disappearance of color in the urine. At the end of the four days no fluid is to be taken, and at the beginning of the fifth day the morning specimen of urine is taken and sent to a laboratory, or a urine specimen is taken every hour, for four hours for concentration record. At the beginning of the fifth day is a good time to take a specimen of blood for chemical analysis, and to have a basal metabolism test run. The physician making a functional survey and giving other physiologic tests can do so on the background of this record.

Medical science still has many tasks before it,—among them is the combination of laboratory tests, clinical data, life records, life management for the services of preventive and constructive geriatrics. Much of this is now in the making. There are needed careful attention and study by the farsighted physician who is interested in lives as well as diseases. And foremost in the field of progressive geriatrics is a thorough understanding and appreciation of the importance of good food and nutrition.

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EFFECTS OF COMPOUND E

While some may consider that the influence of hormones on disease is not directly related to problems of nutrition, the ultimate effects of nutrient substances as well as of hormones are so closely integrated in the body that the nutritionist is wise to keep abreast of significant developments in the endocrine field. The reported effects of compound E (17-hydroxy-11-dehydrocorticosterone) on rheumatoid arthritis and on other disorders are so striking that they deserve comment here.

Dr. P. S. Hench, who has been a painstaking student of this distressing disease for many years, became impressed particularly with the beneficial effects of pregnancy and of jaundice on the symptoms of this disorder. This observation led him to recognize that, though the pathologic anatomy of rheumatoid arthritis appears to be more or less irreversible, the pathologic physiology of the disease is potentially reversible, sometimes dramatically so. Within every rheumatoid patient, he argued, corrective forces must lie dormant awaiting proper stimulation. Whether or not the disease is initiated by microbic infection, the symptoms and mani-

festations would seem likely to be due to "some basic biochemical disturbance which is transiently corrected by some incidental biologic change common to a number of apparently unrelated events." The "basic biochemical denominator" influencing rheumatoid arthritis could be neither hyperbilirubinemia nor a unisexual (female) hormone since neither of these is common to both pregnancy and jaundice. It is probably not a disintegration product from a damaged liver but might be a biologic compound specific in nature and function, a compound which is normal to the human organism.

In the light of recent investigation it is not surprising that Hench and his associates ultimately came to conjecture that the antirheumatic substance might be an adrenal hormone. Ultimately the opportunity arose whereby compound E of Kendall could be given a trial. It is fortunate, as E. C. Kendall himself points out (*Proc. Staff Meetings Mayo Clinic* **24,** *298* (*1949*)), that a large dose of compound E was used (100 mg.) though the material was and still is very scarce. Had 25 or 50 mg. been used "the whole project might well have failed." In addition, the material was employed in the form of a suspension of crystals. "Had the crystals been larger, the absorption would have been delayed and the result would have been different."

In a preliminary report, P. S. Hench, E. C. Kendall, C. H. Slocumb, and H. F. Polley (*Proc. Staff Meetings Mayo Clinic* **24,** *181* (*1949*)) describe the effects of administration of compound E to 14 patients with severe or moderately severe rheumatoid arthritis. Since the fall of 1948, compound E has been given more or less continuously to 5 patients and for periods of eight to sixty-one days to 9 others. A painstaking effort has been made to study the patients objectively and to carry out adequate controls. Thus a fine aqueous suspension of cholesterol was substituted for compound E in certain cases without the knowledge of the three clinical authors who were evaluating the results.

The changes associated with administration of the compound were remarkable. Within a few days, in each of the 14 patients, there was marked reduction of stiffness of muscles and joints, lessening of articular aching or pain on motion, and significant improvement of articular and muscular function. The appetite also improved rapidly and several patients gained weight on routine general diets. A number stressed the loss of the "toxicity" of the disease and experienced a marked sense of well-being. Joint swellings generally diminished, sometimes fairly rapidly and completely, occasionally tardily and incompletely.

At the same time sedimentation rates, ordinarily greatly increased in this disease, became normal within ten to thirty-five days. Serum proteins were also altered, there being a fall in the abnormally increased serum globulin and a reversion towards normal of the albumin-globulin ratio. Urinary concentrations of 17-ketosteroids were reduced by the use of compound E but remained in the low normal and even subnormal range. The excretion of corticosteroids in the urine was increased. Anemia often accompanies this disease. In 4 patients given the hormone for several weeks the hemoglobin and red cell count increased. Biopsies revealed histologic evidence of healing.

When the control preparation of cholesterol was substituted for compound E, symptoms began to return or to increase promptly, generally within two to four days. Sedimentation rates also usually increased promptly. Renewed administration of compound E was associated with a return of improvement.

Possible signs of toxicity included transient pain in the epigastrium in one patient and transient edema, generally pretibial, in others. One patient would sudddenly gain 4 to 7 pounds within two to four days and then as suddenly lose the excess by way of spontaneous diuresis. There appeared at the same time some acne, mild hirsutism, and round-

ing of facial contour. The patient's menses, always irregular, ceased.

Compound E has also been given to 3 adolescents with acute rheumatic fever (P. S. Hench and co-workers, *Proc. Staff Meetings Mayo Clinic* **24,** *277 (1949)*). Two of the patients were in the first attack and the third was probably in a recurrent attack. In each case there was rapid disappearance not only of the fever, tachycardia, and polyarthritis but also of elevated sedimentation rate and abnormalities in the electrocardiograms. The hemoglobin rose but there was no characteristic effect on the number of leucocytes.

The pituitary adrenocorticotropic hormone (ACTH) was given to 2 patients with rheumatoid arthritis and this was associated with marked clinical improvement essentially similar to that resulting from the use of compound E. Within a few days there was striking reduction in stiffness, pain on motion, and articular tenderness. At the same time, however, there was a sense of exhaustion, transient gas pains, heaviness in the chest, and moderate elevation (22 to 40 mm.) of blood pressure. There were also alterations in the blood and urine chlorides, in electrolytes and the carbon dioxide-combining power of the blood, and in the excretion of 17-ketosteroids and corticosteroids in the urine.

These interesting observations are of far more importance in that they may lead to a better understanding of the pathogenesis of rheumatoid arthritis and of related disorders than because of the immediate therapeutic possibilities. From the latter standpoint it needs to be emphasized that compound E is at present difficult to manufacture and is not available. Furthermore, the possibility of production of serious ill effects such as those simulating the Cushing syndrome must be considered. Whether an advance in therapeutics is made or not, however, it is to be expected that a better understanding of the pathogenic mechanisms involved may be gained.

CHOLINE AND PROTEIN DEPLETION

Experimental animals on diets deficient in protein exhibit a rapid loss of substantial quantities of protein from the liver. This is associated with a decrease in the content of ribonucleic acid and accumulation of fat in the liver (*Nutrition Reviews* **4,** *309 (1946)*; **7,** *71 (1949)*). Chemical and morphologic changes occurring in protein deficiency are accompanied by abnormalities in tests of liver function (V. H. Hough and S. Freeman, *Am. J. Physiol.* **138,** *184 (1942)*). Protein deficient diets used in experiments of this type are likely to be inadequate in their content of choline. By providing supplements of choline to dogs on low protein intakes, Hough, E. P. Monahan, T. W. Li, and Freeman (*Ibid.* **139,** *642 (1943)*) were able to prevent changes in dye clearance and serum phosphatase which had occurred in animals on the low protein diet without supplements of choline.

C.-F. Wang and associates (*J. Lab. Clin. Med.* **34,** *953 (1949)*) report the results of experiments evaluating the effect of protein depletion on liver composition, cytology, and function, as well as on plasma volume and thiocyanate space, in rats on diets containing small and large quantities of choline. The diet was of the purified type and contained no protein. Adequate amounts of all of the B-complex vitamins except choline were provided. The low choline diet contained 30 mg. of choline chloride per 100 g., while the high choline diet contained 500 mg. per 100 g. Diets were fed ad libitum.

Within the first three days on the high choline, protein-free diet there was a loss of 30 per cent of liver weight and a similar decrease in the protein content of the liver. In the following two weeks protein loss by the remainder of the body proceeded at a rate greater than that of the liver. After

this time, loss of protein by the liver and by other body tissues was similar.

Fatty acids and glycogen accumulated in the liver of rats on the low choline diet during the first several weeks. There was, therefore, no decrease in liver weight during this period, although the protein loss from the liver was comparable to that of animals on the high choline diet.

Microscopic examination of sections of liver gave evidence of enlargement of parenchymal cells, cytoplasmic condensation, accumulation of fat and glycogen within the cells, and decrease in basophilic granules during the first weeks of the deficiency. Engorgement of cells with fat was more marked in animals on the low choline diet, as were most of the other morphologic changes described. Abnormalities observed in sections of liver from animals on the high choline diet became less marked as depletion was prolonged.

Clearance of bromsulfalein from the blood, which was used as a test of liver function, fell markedly during protein depletion in both groups of animals. However, when clearance and dosage of the dye were expressed in terms of milligrams per 100 g. of body weight it was found that the decrease in clearance was accounted for by loss of body and liver weight. There was no real evidence of malfunction of residual liver cells.

Plasma volume and thiocyanate space were decreased proportionately to the decrease in body weight during the early phases of protein depletion. After about forty days the thiocyanate space expressed as percentage of body weight increased, indicating edema formation. It was of interest to note that the increase in volume of this fluid space occurred at a time when total plasma protein was increasing, a change opposite in direction to what might have been anticipated.

The observations presented indicate that in prolonged protein deficiency there is a loss of retrogressive changes and a return toward normal liver structure and composition. Initial consequences in the liver are severe. An adaptive mechanism, which is facilitated by addition of choline to the diet, then seems to protect this organ.

There is no evidence in the observations of Wang and co-workers that this is to the functional advantage of the liver. It is not suggested that choline replaces protein. Most low protein diets are also low in content of this member of the vitamin B-complex. Therefore, addition of choline to the diet precludes the contribution of a second nutritional deficiency to that under investigation.

VITAMIN A INTAKE AND PHYSIOLOGIC PERFORMANCE IN RATS

In a previous review (*Nutrition Reviews* **3,** *293 (1945)*) the experiments of H. C. Sherman and co-workers showing the favorable effects of high vitamin A intakes on the life span and reproductive performance in rats were discussed. In long-term experiments it was found that in rats fed 3, 6, or 12 I.U. of vitamin A per gram of air-dry food, the rate of gain in weight, the length of life, and the "useful" segment of the life cycle—from the attainment of maturity to the onset of senility—all were increased at the highest level of vitamin A intake.

The optimum level found in these experiments, 12 I.U. per gram of food, was from five to ten times the amount of vitamin A required to protect the rat from all signs of pathology due to vitamin A deficiency, and about four times the level accepted as the minimum adequate for this animal.

Thus there appeared to be a wide range between the amount of vitamin A required just to prevent the signs and symptoms of deficiency and the amount that leads to optimum health. It is also known, however, that at extremely high levels of intake (for

example, 10,000 I.U. per gram of food) vitamin A becomes toxic in experimental animals and in man (*Nutrition Reviews* **5,** *49 (1947)*)

H. C. Sherman and H. Y. Trupp (*J. Nutrition* **37,** *467 (1949)*) have now concluded a further investigation which relates to this question. Having established that 12 I.U. of vitamin A per gram of food gave the most desirable results of any previously tried, they were interested in determining whether this represented a *point* of optimum response, or whether there was a *plateau* of levels at which vitamin A could be fed and still secure optimum response. For this purpose they have compared growth, life span, reproductive performance, and age at death of large, matched groups of male and female rats kept throughout life on diets containing either 12 or 24 I.U. of vitamin A per gram. The lower level is that previously found to be optimal.

Results showed that this increase in vitamin A did not measurably influence growth of either male or female rats between the ages of 28 and 56 days. This was also true of later growth and adult size in the female animals. The males, however, grew to slightly lower adult weights on the diet with 24 I.U. than on that with 12 I.U. per gram of food. In the length of reproductive life, the number of young born, the number of young reared, and the total weight of young at 28 days, slightly higher (more favorable) records were made by the females receiving the lower level of vitamin A. This was also true of length of life, which was appreciably longer in males fed the lower level of vitamin A (715.9 ± 14.93 days versus 646.7 ± 20.54 days, where the figures refer to the average length of life plus or minus the probable error, as calculated from the individual variations from the average), but only slightly longer in the females (794.1 ± 18.01 versus 777.0 ± 18.27 days).

Whether these small differences are more than accidental is not known, the authors view their chief significance as demonstrating that the nutritional response to vitamin A has essentially "plateaued" at these levels of intake. Since the vitamin A was fed as a highly refined cod liver oil, it is not entirely certain that the slight differences which were noted were, in fact, due to an increased intake of vitamin A rather than to other components of the cod liver oil. The authors noted no evidence in favor of the latter assumption, however. Increased liver storage of vitamin A did occur at the higher level of intake.

As in previous papers from the same laboratory, the data of the present paper show clearly that quadrupling a minimum adequate allowance of vitamin A may increase the normal length of life in rats by 10 to 12 per cent, and postpone the onset of old age.

BALANCE STUDIES WITH FOLIC ACID (PTEROYLGLUTAMIC ACID) IN MONKEYS

The metabolic fate of the various vitamins when these are ingested by animals is an interesting topic about which too little is known. Especially is this true of the more recently discovered vitamins. With folic acid, for example, it became apparent early that the urinary excretion of this substance by man amounted to less than 1 per cent of the probable dietary intake. As increasing amounts of the vitamin are fed to man, the proportion of the dose excreted increases; and at comparatively high dosage levels (for example, 3 to 10 mg.), as much as 28 to 56 per cent of the test dose may be recovered in the urine. Nothing is known of the disposition of the fraction not so recovered (*Nutrition Reviews* **6,** *125 (1948)*).

P. L. Day and J. R. Totter (*J. Nutrition* **36,** *803 (1948)*) have reported results of complete balance studies on folic acid (pteroylglutamic acid, PGA), in rhesus monkeys, which are of interest in this connection.

The animals, after a preliminary observation period, were placed upon a PGA deficient diet, then fed as daily supplements (a) 100 micrograms of PGA, (b) 2.5 g. of yeast extract which contained the equivalent of 100 g. of PGA bound as the conjugate (heptaglutamate), or (c) 1000 micrograms of PGA. Daily urine and fecal collections were made, and the free and combined (conjugated) PGA determined by assay with Streptococcus faecalis and Lactobacillus casei before and after treatment with conjugases from hog kidney, chicken pancreas, or rat liver.

Results showed that the total PGA (free and combined) excreted by the monkeys was low and very similar, whether the animals were receiving zero or 100 micrograms of PGA per day, or the 2.5 g. of yeast extract. Only about 1 microgram of PGA (all free) per kilogram of body weight was excreted in the urine daily on each of the three supplements. About 8 to 10 micrograms, mostly free, were excreted with the feces in all three groups.

From previous studies, it had been estimated that 100 micrograms daily of PGA was the minimum dose fully protective against PGA deficiency in animals fed this ration. It is thus apparent that in monkeys, feeding the minimum protective dose produces no significant increase in the excretion of folic acid. An animal fed 1000 micrograms daily of PGA excreted only about 20 micrograms of this substance daily, the increased excretion appearing mostly in the urine. On subsequently dropping the intake of this same monkey to 100 micrograms per day, the excretion fell to the same level previously found. A tenfold increase in the amount ingested over the daily requirement for the vitamin, thus resulted in only a very slightly increased excretion over basal levels—about 10 micrograms, or 1 per cent of the dose. This low excretion was not increased by daily administration of 1000 micrograms of PGA over an eighty day period, hence the low urinary return did not appear to be due to tissue storage of the extra folic acid.

This low percentage urinary return of a large daily dose of PGA is in sharp contrast to the response of the normal human adult, who excreted 30 to 50 per cent of a 5 mg. oral dose within twenty-four hours. The difference may serve to emphasize the differences in metabolism of this (and, perhaps, by extension, other) vitamin from one species to another.

The authors suggest that the apparent lowered excretion by monkeys, as compared with human beings, whatever its cause, may be a reflection of the peculiar susceptibility of the young rhesus monkey to PGA deficiency. It has not yet been shown, however, that young of the human species would not show the same "peculiar susceptibility" to this deficiency if kept upon diets appropriately low in folic acid. Similarly, excretion experiments on children have not been made with this vitamin.

REVERSAL OF THE METABOLIC CHANGES DUE TO IMMOBILIZATION

During convalescence from an acute illness in a previously healthy person certain catabolic changes occur, last for a variable time, and are subsequently followed by an anabolic period during which reversal of the metabolic alteration occurs. During the period of catabolism the nitrogen balance is persistently negative resulting in a loss of body protein and of tissue and, further, there are significant losses of sulfur, calcium, phosphorus, and potassium from the body. The significance and interpretation of these phenomena have been the subject of recent investigations and it has been proposed that changes in adrenal hormone elaboration may account, at least in part, for the metabolic

aberrations observed. Much of this work has been reviewed (*Nutrition Reviews* **3,** *40, 86, 253 (1945);* **4,** *6 (1946);* **5,** *46 (1947)*).

That disuse of a part leads to atrophy of varying degrees has long been known; indeed prolonged rest and inactivity following illness and injury have recently been repeatedly criticized as unphysiologic and leading to prolonged convalescence. With these facts in mind, J. E. Deitrick, G. D. Whedon, and E. Shorr (*Am. J. Med.* **4,** *3 (1948); Nutrition Reviews* **6,** *146 (1948)*) conducted studies of immobilization which demonstrated that definite catabolic changes occurred following immobilization of healthy subjects in plaster casts. The extent of the changes was not as great as that following acute illness or injury but they were qualitatively similar. Nitrogen retention diminished or negative nitrogen balance even appeared. Urinary and fecal calcium and phosphorus excretion increased, leading to the possibility of urinary stone formation. Urinary sulfur excretion increased in proportion to the urinary nitrogen excretion. Thus, it was clear that specific catabolic abnormalities appeared in healthy individuals following simple immobilization in a plaster cast.

The authors have subsequently considered the possibilities of ameliorating these changes observed during immobilization. G. D. Whedon, J. E. Deitrick, and E. Shorr (*Am. J. Med.* **6,** *684 (1949)*) chose the Sanders oscillating bed as a possible means of preventing the changes noted.

Three of the 4 healthy young men previously studied were given a constant dietary intake during and following a five week period of immobilization in plaster casts. The preimmobilization control period lasted for from four to five and a half weeks. The 3 individuals were placed on the oscillating bed at the beginning of the period of immobilization with the bed in motion for eight hours a day in 2 individuals and twenty-one hours a day in the third. The physiologic and metabolic studies carried out in the previous study were repeated on these individuals. The results were considerably different from those observed before. Thus, although nitrogen, calcium, phosphorus, and sulfur excretions increased during the period of immobilization, the increases were considerably less than when still beds were used; in fact, on the average, approximately one-half as much of these substances was lost in the urine as had been previously observed. In addition, postural hypotension and syncope which had been previously observed were absent, indicating that the mechanisms for maintaining the circulation when the erect posture was assumed appeared to be operating at much greater efficiency than when the individuals were maintained on the still bed.

From these studies the authors concluded that the physiologic and metabolic effects of prolonged immobilization could be prevented to a considerable degree by the use of the oscillating bed. As they point out themselves, however, these studies were done in normal individuals and it cannot be concluded from the results that the oscillating bed technic will prevent similar changes from occurring during immobilization from such pathologic states as fractures and severe burns. There was no evidence that the longer period of oscillation was more effective than the shorter. The authors felt that an increased circulation through the extremities and partial weight bearing during the oscillation of the bed might account for some of the ameliorating effects upon immobilization.

POTASSIUM METABOLISM IN DISEASE STATES

Potassium is the predominant cation in the body cells, but in the blood serum sodium is present far in excess of potassium. Thus, in muscle there are approximately 320 mg.

of potassium per 100 g. of muscle, while there are only 19 or 20 mg. of sodium per 100 ml. of blood serum. In the cells, potassium is closely associated with glycogen and with protein. When marked dehydration occurs, or when cells are injured, potassium migrates into the blood serum and sodium in the reverse direction, into the cells.

In diabetes controlled with insulin, if the insulin is withdrawn, negative nitrogen, phosphorus, and potassium balances appear (D. W. Atchley *et al.*, *J. Clin. Invest.* **12,** *297 (1933)*). Indeed, in diabetic acidosis high serum potassium concentrations are frequently observed. During therapy a rather precipitous fall in serum potassium occurs, which then returns to normal levels usually within two or three days.

During the period of low serum potassium concentration muscular weakness may ensue and, in fact, complete paralysis, except of the respiratory muscles, has been observed occasionally. In addition, cardiac enlargement, a high venous pressure, and a high pulse pressure are sometimes seen. Therapy with potassium has been observed to produce rapid improvement. These abnormalities of potassium metabolism in diabetic acidosis were reviewed (*Nutrition Reviews* **5,** *315 (1947)*). Presumably the low serum potassium during recovery may be related to its migration into the cell and fixation with newly formed glycogen and perhaps protein. Sodium accumulated in the cell during the period of acidosis presumably leaves the cell and enters the serum again in exchange for the potassium.

Further studies to elucidate the changes in serum potassium concentration in diabetes have been made by L. Greenman *et al.* (*J. Clin. Invest.* **28,** *409 (1949)*). Nine patients were studied during eleven admissions for diabetic acidosis. Children comprised the majority of the patients, while 2 were young adults. Treatment was with insulin, glucose, saline, but little, if any, potassium.

During therapy, a striking decline in serum potassium occurred in all instances, sometimes reaching rather low levels. Despite this there was, for a considerable time, a continued excretion of potassium in the urine. In addition to this observation, two others of importance were made.

First, during the first few hours of therapy when glycogen was being laid down and when nitrogen balance was becoming less negative, or even positive, potassium continued to be lost from the cells. Second, also, during this period when potassium-free solutions were being administered parenterally there was an expansion of the extracellular fluid. The cellular balances of potassium were made with the help of the relation between nitrogen and potassium; that is, that 1 g. of nitrogen is associated in cells with 2.38 milliequivalents of potassium. Although this relation is true for the direct analysis of normal muscle tissue, a number of observers have failed to find good correlation between nitrogen balance and potassium balance, even in long-term studies. Direct measurement of intracellular potassium concentration would appear to be necessary to elucidate this problem.

Actual studies of electrolyte changes in muscle tissue in man have been made by G. H. Mudge and K. Vislocky (*J. Clin. Invest.* **28,** *482 (1949)*). The patients studied included 3 controls, 3 with gastric alkalosis, and 3 with chronic renal acidosis. Muscle biopsies were taken in the ill patients from the hamstrings or gastrocnemii and averaged 2.4 g. in weight. In the controls, the muscle specimens were obtained at operation under general anesthesia.

The serum potassium levels confirming the several other studies (*Nutrition Reviews, loc. cit.*) were low in all instances of acidosis and alkalosis, with one exception, which was within the lowest normal limits. There was a distinct, often striking, reduction in intracellular potassium in these individuals and a corresponding increase in the muscle sodium content. In this way the sum of the intracellular sodium and potassium remained essentially constant and the same as in

muscle from the control individuals. The authors believed, with evidence from a balance study, that the changes in the intracellular electrolytes were not related to the acidosis or alkalosis *per se* but rather to a negative potassium balance common to both conditions.

One patient with renal acidosis on the day the biopsy was obtained actually developed paralysis, and was unable to feed herself, walk, or turn over in bed. Rapid improvement with disappearance of paralysis occurred following administration of parenteral and oral potassium chloride. Although the muscle potassium content was low in this individual, another patient with considerably lower content did not have paralysis; thus there was not a strict correlation between the muscle potassium content and the neuromuscular signs and symptoms.

Further studies by Greenman and collaborators (*loc. cit.*) were made in an effort to account for these changes in potassium metabolism. In some instances the authors were able to account for the entire fall in serum potassium concentration by expansion of the extracellular fluid due to dilution with the potassium-free fluid which was administered. In addition, the continued urinary losses of potassium added their share in some instances. It thus appears that in diabetic acidosis a low serum potassium concentration, which may be dangerous in itself, occurs due to dilution of potassium in the body fluids by administration of potassium-free fluid, by continued urinary loss of potassium, and, if the calculations are correct, despite a continued loss of potassium from the cells even during the laying down of new glycogen and protein.

Other disease conditions, such as severe diarrheas, persistent vomiting, and especially intestinal obstruction, may also lead to low serum potassium (*Nutrition Reviews* **7**, *3 (1949)*). A study of the changes in serum potassium concentration in 15 patients with acute intestinal obstruction has been made by S. Bellet, C. S. Nadler, P. C. Gazes, and M. Lanning (*Am. J. Med.* **6**, *712 (1949)*). In these patients electrocardiographic changes characteristic of potassium deficiency were observed in association with low serum levels of this cation.

The authors found that the serum potassium level could be brought to normal and the electrocardiographic changes reversed by parenteral administration of potassium or by giving food by mouth. The loss of potassium in these individuals with intestinal obstruction was presumably due to continued excretion of potassium into the gastrointestinal tract and persistent vomiting which continued in the patients studied for periods of from one day to one month. Marked weakness was observed in many of these individuals during the time when low potassium was found in the serum. No definite evidence of paralysis was noted by these authors.

The syndrome of severe potassium deficiency has also been observed in certain instances of chronic nephritis. It is, thus, a clinical syndrome of importance to recognize and is an indication for therapy with potassium. When possible, such therapy should be given as food by mouth, for the body is better able to handle potassium administered that way. In fact, too rapid administration of potassium by the parenteral route may lead to potassium intoxication, a condition closely resembling that of potassium deficiency in clinical signs and symptoms, and an equally, if not more dangerous one as well.

ANEMIA AND EDEMA IN CHRONIC CHOLINE DEFICIENCY IN RATS

The relation of choline to various forms of anemia is not clear at the present time. Repeated administration of moderate doses of this compound, especially with simultaneous

administration of fat has been reported to produce a hemolytic type of anemia in both man and dogs (*Nutrition Reviews* **5,** *116, 148 (1947)*). On the other hand are various reports of beneficial effects of choline administration in certain cases of refractory megaloblastic anemia in man (*Ibid.* **6,** *89 (1948)*).

Both P. J. Fouts (*J. Nutrition* **25,** *217 (1943)*) and J. M. McKibbin, S. Thayer, and F. J. Stare (*J. Lab. Clin. Med.* **29,** *1109 (1944)*) have reported lowered hemoglobin levels in dogs fed choline deficient diets, but this phenomenon has apparently not been widely observed in other experimental animals.

R. W. Engel (*J. Nutrition* **36,** *739 (1948)*) reported a careful study of the effects of chronic choline deficiency on hemoglobin levels in rats. Rats, 23 days of age, were placed on various choline-low diets adequate in other vitamins and containing varying levels of protein. Sufficient choline was fed during the first month to prevent development of fatal kidney hemorrhages. Hemoglobin determinations were made at least once monthly over a twenty-four week period. In all cases, a lowered hemoglobin level with a range of 6.25 to 11.95 g. per 100 ml. of blood was observed in animals maintained on the choline-low diets for three months or longer.

Anemia developed rather rapidly from the sixth to the tenth week of feeding, then remained essentially unchanged over the ensuing fourteen week period. The severity of this anemia was associated with the protein content of the diet, the lowest hemoglobin levels being found in animals receiving the diets lowest in protein. Some anemia, however, was evident even in the animals receiving 19 per cent of protein in the diet.

In all cases, and even at the lowest level of protein intake (7.5 per cent of the ration) supplementation of the ration with choline prevented development of anemia and normal hemoglobin levels (13.45 to 14.65 g. per 100 ml. of blood) were obtained. Curative experiments with choline were not reported; folic acid, however, was ineffective in curing the anemic condition. Methionine, like choline, was effective in preventing the anemia at the one level of protein at which it was tested.

Another observation of considerable interest was that 7 of 12 animals on the choline-low diet containing only 7.5 per cent of protein, developed a marked edema, characterized by accumulation of fluid in the abdominal and thoracic cavities as well as in the subcutaneous tissues. This condition was not observed in any of the animals receiving the same diet supplemented with adequate protein.

In explanation of the anemia-preventing action of choline on these diets, the suggestion that it acts by sparing methionine is advanced. This is consistent with the finding that methionine was also effective in preventing the anemia, and can be correlated with other reports of the favorable effects of methionine in hematopoiesis (for example, F. S. Robscheit-Robbins, L. L. Miller, and G. H. Whipple, *J. Exp. Med.* **85,** *243 (1947)*), and of the development of anemia in rats on low methionine diets (for example, A. A. Albanese, L. E. Holt, V. Irby, and J. E. Brumback, *J. Biol. Chem.* **165,** *179 (1946)*). However, the suggestion does little to clarify the fundamental biochemical defect responsible for production of the anemia.

Is choline (and methionine) preventive because in its presence more methionine is available for formation of blood proteins and possibly other specific functions? The argument would appear to work as well in reverse, since methionine also spares the requirement for choline. The apparently general occurrence of anemia in animals fed choline-low diets, whatever its explanation, should stimulate interest in a more exact assessment of the role of this nutritional factor and of methionine in the etiology and treatment of the variety of anemias which afflict man.

PROTEIN DEPLETION AND THE EFFECT ON FLUID DISTRIBUTION

Deficiency of protein in the diet is associated with changes in fluid balance and the formation of edema. E. H. Starling (*J. Physiol.* **19,** *312 (1895)*) elaborated the hypothesis that the decrease in plasma protein following inadequate protein intake results in a fall in plasma colloid osmotic pressure, decreased ability to retain water in the capillaries, and a diffusion of fluid into tissues. For nearly a half century the validity of this concept was not seriously questioned. However, recent observations have pointed out that nutritional edema may occur without any significant decrease in plasma colloid osmotic pressure (*Nutrition Reviews* **4,** *317 (1946)*; **5,** *31 (1947)*).

S. E. Dicker (*Biochem. J.* **43,** *444 (1948)*) has studied the sequence of events in the redistribution of body fluid in adult rats fed diets inadequate in content of protein. The low protein diet was made up largely of fresh turnips and contained less than 0.7 per cent protein. The caloric content was low. Supplements of niacin, riboflavin, thiamine, and vitamin A were provided.

Control animals were given a standard diet adequate in protein and calories, and containing 18 per cent casein as a protein source. Other groups of rats were provided a low protein, high carbohydrate diet. The level of protein in this diet was 0.5 per cent, comparable to that of the first diet. However, the caloric intake of animals on this diet was higher and identical to that of rats on the control diet. All rats were fed for four weeks on the standard diet before being placed on an experimental diet.

The concentration in plasma of total protein, albumin, globulin, water, chloride, sodium, potassium, and nitrogen, as well as the colloid osmotic pressure, was determined at intervals. In addition, analyses were made of three body tissues, liver, muscle, and brain, to determine the content of water, chloride, sodium, and potassium. The extracellular fluid phase was calculated on the basis of the chloride and sodium content of a tissue. It has been amply demonstrated that these elements are mainly extracellular. Intracellular space was estimated by difference, subtracting the calculated extracellular space from the water content of the tissue.

Rats fed for seven days on the turnip-low protein diet retained normal values for the content of water in plasma and in tissues, plasma protein concentration, and plasma osmotic pressure. However, the extracellular fluid phase had increased 50 per cent in liver and 44 per cent in muscle, giving evidence of tissue edema although the concentration of plasma protein and colloid osmotic pressure remained normal.

After fourteen days on this diet there was a marked increase in plasma water and a significant decrease in plasma protein concentration. The plasma colloid osmotic pressure was decreased to 16.3 cm. water as compared with an average pressure of 19.6 cm. water in the control rats. There was a further increase in the extracellular fluid of the muscles.

The direction of these changes was maintained so that at the end of six weeks on this diet the concentration of plasma protein had decreased to 5.02 g. per 100 ml. It was 7.06 g. per 100 ml. in the control animals. The plasma colloid osmotic pressure was decreased further to 10.2 cm. of water. The extracellular fluid space of muscle was more than two and a half times that of the control. In liver the increase was 50 per cent, while the extracellular space of brain was not changed significantly. With the development of protein deficiency and an increase in extracellular space there was progressive decrease in the intracellular fluid. Tissue edema developed concurrently with a marked loss of intracellular water.

Rats fed the low protein, high carbohydrate diet which provided a more adequate caloric intake exhibited similar redistribu-

tions of fluid. The progression of the changes was somewhat slower, however.

These interesting experiments demonstrate that the onset of edema on low protein diets is independent of change in colloid osmotic pressure of plasma. At a later stage, further increases in extracellular fluid space coincided with progressive decrease in the plasma colloid osmotic pressure. There was even then, however, no clear correlation between the degree of hypoproteinemia, the fall in colloid osmotic pressure, and/or the magnitude of the extracellular fluid phase of tissues.

It is of interest to point out that V. Hollander, P. Chang, and Co Tui (*J. Lab. Clin. Med.* **34,** *680 (1949)*) measured extracellular fluid as thiocyanate space and total body water using deuterium oxide in depleted human subjects. Their findings indicate an increase in extracellular fluid and a probable decrease in intracellular water in human beings with protein depletion.

In another paper, S. E. Dicker (*Biochem. J.* **43,** *453 (1948)*) reports the results of experiments designed to evaluate the changes in extracellular and intracellular fluid of tissues of normal and hypoproteinemic rats during water diuresis. The diets of the animals and the procedures used were similar to those described above. The hypoproteinemic rats had been on the turnip-low protein diet for six weeks before testing.

Both the control and hypoproteinemic animals were given food but no water for twenty-four hours before the provision of water for diuresis. The standard quantity of water given was equivalent to 5 per cent of the body weight. This was given by stomach tube. The animals were killed at intervals of fifteen, thirty, forty-five, sixty, seventy-five, ninety, and one hundred and twenty minutes after administration of the standard amount of water. In both control and hypoproteinemic rats water absorption from the intestine was completed within sixty minutes. There was a delay between the height of water absorption and the height of diuresis.

Dicker discerned three distinct phases in the handling of water in the normal rats. The early or absorptive period was characterized by dilution of plasma and decrease in extracellular fluid. This was followed by an excretory period in which diuresis reached its height and there was an increase of extracellular fluid but a decrease in intracellular fluid phase of tissues. In the final period there was a return to normal fluid distribution.

The results of the administration of similar quantities of water to hypoproteinemic rats were remarkably different. Diuresis was delayed in its onset and the volume of urine was much less. There was no dilution of plasma or increase in water content of plasma during the absorptive phase. There were no demonstrable changes in extracellular or intracellular fluid. A large accumulation of fluid occurred in these animals that had not been observed in any of the control rats. The perirenal and retroperitoneal connective tissues became so distended with fluid that on gross observation they were found to be taut and gelatinous in consistency. In several rats there were similar accumulations of fluid in the mediastinal connective tissue. It would seem that tissues such as the muscle and liver are unable to hold the extra water. Therefore the fluid collects in deep connective tissue.

It might be argued that neither chloride nor sodium content of a tissue provides a wholly accurate measure of extracellular fluid. However, these methods of determination certainly provide an approximate measure of this fluid compartment. The relative size of the extracellular fluid space changed significantly during the course of these experiments. It can be reasonably stated that the Starling hypothesis does not adequately explain the redistribution of body fluids occurring in nutritional edema.

Factors other than the plasma colloid os-

motic pressure must have a determining role in the initiation of the fluid shift and the accumulation of water in the extracellular space. Other factors which might conceivably be parts of this mechanism include the physical character of the capillary wall, antidiuretic hormone, adrenal cortical hormones, and ion exchange in and about tissue cells. The control of fluid distribution in the body takes the character of a complex with many substances apparently impinging on the mechanism. With the Starling hypothesis having been demonstrated to be inadequate, great interest will attend new observations assessing the importance of other factors in the production of edema.

PRODUCTION, PREVENTION, AND TREATMENT OF DIETARY LIVER INJURY

In the past decade much attention has been focused on dietary liver injury. P. György and H. Goldblatt were pioneers in this field and have continued their work over many years. A recent presentation of their data contains several points of interest (*J. Exp. Med.* **89,** *245* (*1949*)).

Two distinct forms of liver injury, necrosis and fibrosis (cirrhosis), may be found when diets low in lipotropic substances are fed to rats (*Nutrition Reviews* **3,** *122* (*1945*)). In their experiments acute necrosis occurred with a variable frequency which they could not correlate completely with the absolute or relative content of cystine or methionine in the diets used. Their best diets produced acute necrosis in about 50 per cent of the animals, most of the remainder developing diffuse hepatic fibrosis.

Acute necrosis could be largely prevented by supplements of cystine, methionine, or yeast, whereas choline and liver extract appeared to enhance the necrosis. Cystine in large doses also exaggerates this condition (*Nutrition Reviews* **1,** *88* (*1943*)). However, a deficiency of cystine or methionine alone was not a sufficient condition for development of these lesions. The type of dietary fat also appeared to affect the incidence of necrosis. Cod liver oil and, to some extent, lard promoted necrosis, whereas Crisco and butter were protective.

These effects could be accounted for in part by the tocopherol content of these fats. Addition of tocopherol to their necrosis-producing diets had a protective action equal to that of cystine or methionine thus confirming the original report of K. Schwarz (*Z. f. physiol. Chem.* **281,** *109* (*1944*); *Nutrition Reviews* **6,** *118* (*1948*)). As much as 30 mg. of tocopherol were given daily in some experiments since Schwarz (*loc. cit.*) reported that tocopherol in amounts which should prevent the usual specific manifestations of vitamin E deficiency may not suffice to prevent the development of acute necrosis. E. L. Hove and P. L. Harris (see *Nutrition Reviews* **6,** *118* (*1948*)) have shown that alpha-tocopherol improves the utilization of protein under certain circumstances. It has also been shown (Hove, *Arch. Biochem.* **17,** *467* (*1948*)) that tocopherol is protective against the hepatotoxic action of carbon tetrachloride. Whether the mutual interchangeability of tocopherol and the sulfur-containing amino acids is due to a mutual "sparing" action, or whether they may each act as detoxifying agents cannot be stated at this time. Further experiments along this line seem indicated.

In addition to the tocopherol content of these fats, their relative concentrations of unsaturated fatty acids appeared to be important. Cod liver oil and lard contain large amounts of unsaturated fatty acids while Crisco and butter contain very little. The possibility is advanced that unsaturated fatty acids may increase the incidence of necrosis by promoting destruction of tocopherol in the body. This possibility also needs further investigation.

In contrast to acute necrosis, dietary cir-

rhosis could be produced with great regularity. Cystine promoted, while methionine, choline, liver extract, choline plus cystine, or yeast prevented the condition. Thiouracil also will prevent these lesions (*Nutrition Reviews* **4,** *79* (*1946*)). Lard and cod liver oil promoted while Crisco and butter retarded development of cirrhosis. Rice appeared to have a protective action when compared with a similar diet containing sucrose as a source of carbohydrate. Tocopherol had no detectable influence in preventing cirrhosis even when used in large doses.

Although the pigment ceroid was regularly found with most of the diets used, cirrhosis without ceroid could be produced when cod liver oil and, to a less degree, other sources of unsaturated fatty acids were eliminated from the diet. Other investigators have reported similar results (*Nutrition Reviews* **4,** *137* (*1946*)). Tocopherol had but a slight influence on the deposition of ceroid. Other workers have recorded variable results, some obtaining nearly complete inhibition of ceroid deposition with tocopherol. The reason for these differing results is not evident.

György and Goldblatt originally held to the belief that the fibrotic changes in experimental dietary cirrhosis began in the portal spaces. Further study has now led them to the conclusion that these changes begin around the central vein, as recognized by L. L. Ashburn, K. M. Endicott, F. S. Daft, and R. D. Lillie (*Am. J. Path.* **23,** *159* (*1947*)). In later stages the fibrosis may be both portal and nonportal in distribution. Dietary cirrhosis in rats thus differs in this important respect from Laennec's cirrhosis in man which is generally believed to be portal in origin.

It should be noted that György and Goldblatt used basal diets which did not contain some of the "B vitamins" recently shown to be essential for the rat under certain conditions, i.e., niacin. folic acid, and vitamin B_{12}. Niacin deficiency has been reported to develop regularly in low casein, cystine supplemented rations (J. M. Hundley, *J. Nutrition* **34,** *253* (*1947*)). Low casein rations have also been reported to produce a folic acid deficiency (A. Kornberg, F. S. Daft, and W. H. Sebrell, *Science* **103,** *646* (*1946*)). The fact that liver extract and yeast, both of which contain some of these vitamins, exerted a definite effect on both cirrhosis and necrosis seems to render this point especially pertinent.

Even from this brief and incomplete consideration of the many facts presented and questions raised by this study, it is evident that the etiology of dietary necrosis and cirrhosis in rats is a complex phenomenon. The etiology of cirrhosis of the liver in man is probably even more complex. It is perhaps understandable that lipotropic therapy of human cirrhosis has not proved to be the simple remedy for which one might hope (*Nutrition Reviews* **6,** *298* (*1948*)).

While it is clearly established from animal experimentation that a diet deficient in lipotropic factors will produce liver cirrhosis, and that these lesions can be prevented by appropriate supplementation of the diet, it is less clear to what extent a liver already damaged can return toward normal with lipotropic therapy. Dietary factors which assure prevention of a pathologic condition may not necessarily be beneficial in its treatment since secondary complications may develop and irreversible tissue damage may have occurred. Despite its obvious practical implications, this subject seems to have been studied less in animals than in man. There are two reports in the literature on this subject (J. V. Lowry *et al.*, *Pub. Health Reports* **56,** *2216* (*1941*); Lowry, L. L. Ashburn, and W. H. Sebrell, *Quart. J. Studies on Alcohol* **6,** *271* (*1945*)). These workers studied a series of about 40 rats treated with choline or casein. Their observations indicated that lipotropic factors would accelerate regeneration of liver cells, reduce fat infiltration, and improve the histologic appearance of the liver parenchyma but had no effect on the diffuse fibrosis.

P. György and H. Goldblatt (*J. Exp. Med.*

90, *73 (1949)*) have studied this subject again with results which vary somewhat from those mentioned above. Rats were maintained on the cirrhosis-producing diets for about a hundred and fifty days. At the end of this period, lipotropic therapy was started and continued for seventy-five to a hundred and fifty days. Treatment consisted of daily supplements of methionine (50 mg.), cystine (50 mg.) plus choline (20 mg.), liver extract (0.2 g. of crude liver extract), thiouracil (0.1 per cent in the diet), or substitution of a diet rich in casein and low in fat for the original diet.

In one group of 76 rats, laparotomy biopsies were done at the end of the cirrhosis-producing period. An attempt was made to select a section of liver which showed the greatest degree of fibrotic changes. The mortality from this procedure was high. The animals dying within a short time after biopsy provided an opportunity for comparison of the biopsy and necropsy pathologic findings. In 28 animals so examined, 10 showed roughly identical findings in the biopsy and necropsy specimens whereas in 18 the fibrotic changes were less pronounced in the biopsy specimen. No instance was found where the severity of the lesions was greater in the biopsy material than in the whole liver examination. These results serve to re-emphasize the caution which must be exercised in interpreting data drawn from a comparison of biopsy and necropsy pathology, and even in successive biopsies from the same animal.

A second group of 25 rats was maintained from a hundred and fifty days on the cirrhosis-producing diet and then treated for a hundred and fifty days with lipotropic therapy. No controls were used.

A third group of 110 rats was maintained for a hundred and twenty days on a diet modified with the intention of producing a milder type of cirrhosis than in groups one and two. Various treatments were then instituted and continued as before. A "control" group was maintained on the basal ration throughout the experiment. Many of these rats died early in the period during which the experimental animals were being treated and only 3 survived to termination of the experiment.

The results of their experiments confirmed, in many details, the results of previous investigators (J. V. Lowry *et al.*, *loc. cit.*). Lipotropic therapy which was effective in prevention was also effective, at least in most cases and to some degree, in therapy. Their results did differ in one important respect from those of Lowry *et al.* These workers had found no effect on the diffuse fibrosis which is the basic pathologic process in these livers. György and Goldblatt on the other hand believe their data indicate that lipotropic therapy does effect a significant reduction in the fibrosis, provided the cirrhosis has not become too severe. Admittedly this is a difficult point to settle since the regression of fibrosis as observed histologically may have been due to stretching, thinning out, and perhaps some condensation of the originally wide, fibrotic bands. In addition, the difficulties in comparing biopsy with necropsy sections as in their first group of animals, the lack of controls in their second group, and the lack of directly comparable controls in their third group make one accept this conclusion with considerable reservation.

From what is known concerning the general behavior of scar tissue in other parts of the body, the burden of proof is certainly on those who claim that such tissue may be made to regress or disappear as the result of any sort of a biochemical influence. On the other hand, their conclusion is supported by reports of other investigators who have observed reduction of scar tissue in livers made cirrhotic with hepatotoxic agents (G. R. Cameron and W. A. E. Karunaratne, *J. Path. Bact.* **42,** *1 (1936)*; T. G. Morrione, *J. Exp. Med.* **85,** *217 (1947)*; B. Steinberg and R. A. Martin, *Arch. Path.* **41,** *1 (1946)*; E. A. Sellers, C. C. Lucas, and C. H. Best, *Brit. Med. J.* **1,** *1061 (1948)*).

In the experiments of György and Goldblatt (*loc. cit.*) best results with lipotropic therapy were obtained using a combination of an adequate amount of casein with methionine or liver extract, and by combination of methionine with liver extract. Methionine and thiouracil, both of which singly are effective in prevention of hepatic cirrhosis, proved to be less effective in treatment when administered together, than methionine given alone. Tocopherol had no apparent influence although large doses of this vitamin were not used.

Their results with lipotropic therapy were, in general, disappointing when treating very severe cirrhosis. The improvement which they did obtain did not occur with complete regularity and prolonged treatment was necessary for maximal results. Lipotropic treatment was, however, almost universally successful in effecting a disappearance of ascites.

Their experiments by no means exhaust the list of possible effective agents which should be tried in nutritional cirrhosis. It is suggested that there may be complicating factors, perhaps hormonal, present in animals with cirrhosis which do not appear in preventive experiments. These possibilities should be tested and other work along these lines should be continued in the hope that a clue may emerge which will render treatment of cirrhosis in man more uniformly successful.

DETERMINATION OF EARLY THIAMINE DEFICIENT STATES IN MAN

On the basis of excellent experimental evidence it is assumed that clinical signs of dietary insufficiency do not become evident for varying periods of time following initiation of an insufficient intake of a particular essential dietary ingredient. During this period of "subclinical" deficiency, the metabolic alterations or structural changes which eventually produce recognizable clinical symptoms of a deficiency state occur. Reliable means for detection of such subclinical deficiency states are badly needed.

A number of such methods for detecting marginal deficiencies of thiamine have been suggested. Among the most thoroughly studied is that described by M. K. Horwitt and O. Kreisler (*J. Nutrition* **37,** *411* (*1949*)). These authors have maintained groups of patients at a state hospital on diets of known thiamine content, suboptimal, marginal, or fully adequate, for periods up to four years (see *Nutrition Reviews* **7,** *264* (*1949*)).

In accordance with the observations of previous workers, the basal blood levels of lactic and pyruvic acids did not correlate well with the state of thiamine deprivation. While there was a definite tendency toward increased basal levels of blood pyruvate as thiamine deficiency progressed, there was much overlapping between the values found in the deficient and normal groups, and only after clinical signs of thiamine deficiency were marked were these values significantly increased.

Subsequently, determinations were made bimonthly sixty minutes following glucose administration. Although the average results with the depleted subjects were significantly higher than those with subjects on an adequate thiamine intake, the individual figures again overlapped, so that the test again was not sufficiently sensitive to permit detection of early abnormality in an individual subject.

Finally, glucose and lactic and pyruvic acid levels were determined following administration of glucose, and mild exercise. The latter consisted in climbing and descending a given number of stairs during a period of approximately one minute. Blood samples were drawn five minutes later, when the increases in lactic and pyruvic acids due to the exercise were at the maximum. The results of this glucose-exercise test showed

a more marked difference among the experimental groups than appeared with glucose alone. However, the levels of lactic and pyruvic acids in patients administered glucose varied with the glucose level in the blood.

Consequently, individuals with high glucose tolerance curves showed higher levels of lactic and pyruvic acids in the blood than did individuals showing low glucose tolerance curves, and glucose tolerance was not related to the thiamine intake. In most individuals ingesting a satisfactory diet, the glucose level of the blood following the glucose plus exercise test was approximately ten times the level of lactic acid, and the latter in turn was approximately fifteen times the level of pyruvic acid. This relation appeared to hold regardless of the nature of the glucose tolerance curve of the individual. It thus became possible to devise an *index of carbohydrate metabolism*, or CMI, calculated according to the formula:

$$\frac{\text{CMI}\left(\text{L}-\frac{\text{G}}{10}\right)+\text{P}\left(15\text{P}-\frac{\text{G}}{10}\right)}{2}$$

where L, G, and P represent the levels of lactic acid, glucose, and pyruvic acid, respectively, all expressed in milligrams per 100 ml. of blood. When this index was calculated for patients who were frankly thiamine deficient, values higher than 15 were uniformly obtained. With patients on a satisfactory thiamine intake, the index was uniformly in a narrow range lower than 15; while those individuals receiving the marginal level of thiamine (400 micrograms per day) showed fluctuating values, sometimes above and sometimes below 15, depending in part upon their physical activity.

To test the applicability of the index to detection of subclinical thiamine deficiency, the index was determined at intervals in patients newly transferred from a thiamine sufficient to the thiamine deficient ration. Every subject in this group went higher than 15 within five months after going on the deficient ration; most of them did so within three months. This occurred in every case weeks before any clinical signs of thiamine deficiency were noted.

Finally, the test was applied to a group of "poor eaters" not previously among the experimental groups before, during, and after eight months of daily supplementation with over 3 mg. of thiamine. None of these subjects showed clinical signs of thiamine deficiency; however, 9 of 33 showed an index of 15 or over. The CMI of all 9 of these patients decreased markedly during the first month of thiamine supplementation; after supplementation, 7 of the 9 had indices below 15 (representing a fall of 4 points or more in each case), one of 16, and one that had decreased from 30 to 20. Of the 24 patients who started with indices below 15, 4 showed decreases in the CMI of more than 4 units, 2 showed small increases, and the remainder were unchanged.

These results indicate that the CMI represents a reliable index for determining whether an individual is suffering from subclinical thiamine deficiency, and as such, should be useful for further research, and perhaps in clinical practice. Thiamine deficiency is not, of course, the only metabolic condition which will elevate the blood levels of pyruvic and of lactic acids. Cardiovascular insufficiencies, liver disorders, emotional states, certain infections, etc., may all bring about increases. These conditions can, however, be ruled out by a competent examiner; the authors plan to determine their effects on the CMI in subsequent work. Their present results show that a riboflavin deficiency sufficiently pronounced to produce skin lesions did not produce significant changes in the CMI.

ROLE OF TRYPTOPHAN IN THE BIOSYNTHESIS OF NIACIN

Tryptophan may substitute for niacin in the diets of certain animals (*Nutrition Reviews* **4,** *334 (1946);* **5,** *247 (1947)*). Some reports (*Ibid.* **7,** *187 (1949)*) point to the conclusion that the tissues of the animal, rather than intestinal bacteria, are the site of the formation of niacin from tryptophan. Other reports, however, have indicated that the bacteria of the intestinal tract may have an important role in this apparent conversion of tryptophan to niacin (*Ibid.* **6,** *233 (1948)*). In this latter review reference was made to a preliminary report of observations which have now been published in detail.

P. Ellinger and M. M. Abdel Kader (*Biochem. J.* **44,** *285 (1949)*) have found that administration of tryptophan to rats is followed by a substantial increase in the urinary excretion of N′-methylnicotinamide chloride, a metabolite of niacin. When 100 mg. of DL-tryptophan were provided by stomach tube, excretion of N′-methylnicotinamide chloride was increased 50 to 100 per cent over control or basal levels. However, when the same quantity of the amino acid was injected intraperitoneally, increase in the urinary excretion of the metabolite was much less, varying from 15 to 30 per cent.

With provision of 1 g. of succinylsulfathiazole in the daily diet the quantity of N′-methylnicotinamide excreted was decreased markedly to about 20 per cent of pretreatment levels. One hundred milligrams of DL-tryptophan given orally to these animals failed to produce a significant increase in excretion of N′-methylnicotinamide. The conclusion seemed warranted that the effect of tryptophan on niacin synthesis was mediated through the bacterial flora of the intestine.

Ellinger and Abdel Kader proceeded to examine the *in vitro* effect of tryptophan on production of niacin by various intestinal bacteria. Although addition of this amino acid to mediums containing casein hydrolysate or ammonium lactate increased growth and acid production of two strains of Escherichia coli isolated from human feces, there was no effect on synthesis of niacinamide by these organisms. Similarly, there was no increase in production of niacinamide when tryptophan was added to cultures of Streptococcus faecalis or various strains of Proteus. When, however, mixed cultures of bacteria from the rat cecum were grown in an ammonium lactate medium addition of DL-tryptophan increased synthesis significantly. This occurred with both aerobic and anaerobic culture of the organisms. In each of these experiments concentrations of niacinamide were determined by microbiologic assay.

Addition of other single amino acids and various methylated compounds to the growth mediums was tested for an effect on the niacinamide produced by E. coli. Of the compounds tested the amino acid, ornithine, in concentrations of 0.001 M. was by far the most efficient, increasing synthesis by 300 to 400 per cent. Of the other substances added to the mediums only arginine and glutamine were associated with increased production of niacinamide by the organism. These changes were relatively small as compared with the effect of ornithine. Ornithine given orally to rats did not increase the N′-methylnicotinamide output. These observations indicated that niacinamide may be synthesized with the provision of tryptophan to mixed cultures of bacteria from the cecum of rats and that ornithine serves as a precursor of nicotinamide for E. coli. Failure of ornithine given orally to influence the urinary output of N′-methylnicotinamide was not considered as a contradiction to the concept that this amino acid is concerned in the biosynthesis of nicotinamide since ornithine is known to be extremely unstable in the mammalian body.

In a later paper the same authors (P. Ellinger and M. M. Abdel Kader, *Nature* **163,**

799 (1949)) record the results of further observations on the bacterial synthesis of nicotinamide. It was demonstrated that niacinamide is synthesized by a strain of E. coli isolated from the intestinal tract of rats in mediums containing ammonium lactate to which tryptophan had been added. Similarly, ornithine added to ammonium lactate medium or to a medium containing phosphate and glucose resulted in increased production of nicotinamide by this organism. Combination of tryptophan and ornithine in the medium gave no increase in nicotinamide synthesis above that when ornithine alone was present.

The enzyme systems responsible for this synthesis were demonstrated to be in the washings of the disintegrated bacterial cells. There was not a demonstrable decrease in concentrations of tryptophan in the mediums following production of important quantities of niacinamide. These observations were interpreted as indicating that tryptophan is not itself a precursor. Rather the concept is offered that tryptophan has the role of a biologic catalyst in the synthesis of niacinamide. It is also suggested that ornithine is an intermediary substance in this biosynthesis. Because tryptophan has no effect in increasing synthesis in the presence of ornithine, the opinion is stated that it catalyzes an earlier stage of the synthesis by influencing formation of ornithine. The fact that administration of increasing quantities of tryptophan to rats is not accompanied by proportional increases in N′-methylnicotinamide excretion, such as occurs with administration of increasing amounts of niacinamide, is taken, also, as evidence for a catalytic rather than a substrate function of tryptophan.

C. Heidelberger, M. E. Gullberg, A. F. Morgan, and S. Lepkovsky (*J. Biol. Chem.* **175,** *471 (1948)*) have reported that the radioactive carbon of DL-tryptophan-B-C^{14} did not appear in the N′-methylnicotinamide of the urine of rats, rabbits, and dogs to which the amino acid had been fed. The proposal of a catalytic function for tryptophan in the biosynthesis of niacinamide must be taken as an interesting new concept of the function of this amino acid. However, additional evidence must be provided before this can be accepted as the established mode of action of tryptophan in the biosynthesis of niacin.

REDISTRIBUTION OF BODY FLUID DURING GROWTH

Water is an essential component of the diet and makes up a large part of the total mass of the body. Its physiologic functions are manifold. Changes in fluid distribution may occur as the result of various physiologic or pathologic mechanisms. Of interest are the changes which occur in water content and distribution during growth. It had been reported that the available fluid volume is greater per unit of body weight in children than in adults (M. Morse, D. E. Cassels, and F. W. Schultz, *Am. J. Physiol.* **151,** *438 (1947)*).

F. X. Fellers, H. L. Barnett, K. Hare, and H. McNamara (*Pediatrics* **3,** *622 (1949)*) attempted more definitive description of changes occurring in the extracellular fluid space during infancy and childhood. Thirty-six individuals varying in age from early infancy to adulthood served as subjects for these experiments. All were free from renal disease and body fluid disturbances.

In approaching this study critical appraisal was given to various methods commonly used for determination of extracellular space. Sodium and chloride ions are largely limited in distribution to this space. The injection of small quantities of radioactive isotopes of these elements permits measurement of extracellular space in human subjects. Thiocyanate and the metabolically inert carbohydrates, inulin, mannitol, and

sucrose, have been similarly used. Extracellular space determined by the use of one of these substances may not give results wholly comparable with those determined by the use of another substance. There are theoretic and practical objections to critical acceptance of the fluid space delineated by any of these methods as being only and wholly extracellular.

Fellers and co-workers compared the results obtained with the use of sodium^{24}, thiocyanate, inulin, and mannitol in the same subjects. The quantity of the material in blood and in urine was determined at intervals following the injection. The fluid space occupied was calculated by dividing the difference in the quantity injected and the quantity excreted, by the serum concentration.

Extracellular space determined by the use of inulin and mannitol continued to increase after injection and did not reach a constant value. These materials were demonstrated to be rapidly excreted by the kidney. The authors state that the failure of mannitol and inulin space to reach constant values was probably because of cumulative errors of large magnitude in determining the amount of the carbohydrates excreted. Experimentally it was demonstrated in dogs that ligation of the renal pedicles and the production of anuria resulted in constant values for inulin space whereas mannitol space continued to increase but at a rate lower than in the intact animal. The explanation given for the progressive increase in mannitol space when renal pedicles were ligated was that the carbohydrate was being slowly metabolized.

In contrast, thiocyanate and sodium are very slowly excreted by the kidney. Extracellular space thus determined reached a constant level after two hours. It was considered, therefore, that the changes in extracellular space determined by use of thiocyanate and sodium^{24} were significant. Mean values for extracellular space determined by these two substances in individuals of similar age and body size were quantitatively similar. To illustrate, the mean space in percentage of body weight for infants weighing from 2.1 to 4.8 kg. was 41.2 per cent and 42.6 per cent for thiocyanate and sodium^{24}, respectively. A progressive decrease in extracellular space was demonstrated as growth continued. Most of the over-all decrease occurred in early infancy, although there was a smaller but definite decrease associated with the period of adolescence. The mean thiocyanate space in 4 adults was 23.1 per cent and the mean sodium^{24} space was 27.1 per cent of body weight.

The authors are fully aware of the difficulties in using thiocyanate and sodium as measures of extracellular fluid volume. They prefer to refer to thiocyanate and sodium space. It is likely, however, that changes in extracellular fluid are related primarily and importantly to the changes in thiocyanate and sodium^{24} space recorded. The only other seemingly possible explanation would be that there was associated with growth a simultaneous shifting of distribution of the two electrolytes into other fluid compartments. This would seem to be an unlikely occurrence. The degree of change observed in growth is one which by comparison with other physiologic mechanisms is relatively great, there being a decrease of 57 per cent in sodium^{24} space and of 70 per cent in thiocyanate space as the human organism progresses from early infancy to attainment of full growth. Since extracellular fluid may by composition be characterized as an ultrafiltrate of blood plasma, the relatively great quantity of this fluid in early life would in consequence provide greater absolute amounts of substances required in the synthesis and deposition of materials composing new tissues elaborated in the growth process.

INCIDENCE OF PELLAGRA

The incidence of vitamin deficiency in the general population of the United States is a much debated subject with few facts to support the debate. Of considerable interest, therefore, is the recent communication of W. B. Bean, R. W. Vilter, and M. A. Blankenhorn (*J. Am. Med. Assn.* **140,** *872 (1949)*). These authors have had an especial interest in pellagra and have made a continued effort over a period of more than thirteen years to diagnose all cases of pellagra admitted to the Cincinnati General Hospital. The diagnosis was personally checked in all cases. Only patients showing florid pellagra with bilateral pellagrous dermatitis and glossitis were included in their report.

Their figures reveal a startling decline in the incidence of this disease beginning in about 1939 and continuing to the present. From 1935 to 1939, 0.95 per cent of all medical admissions had pellagra. In 1939 a total of 34 cases was diagnosed, while in 1940 only 3 cases were found. This decline continued so that in 1946 and 1947 there were no cases on the medical wards and only one case had been seen through July 1948. A similar decrease occurred in the frequency with which a diagnosis of niacin deficiency was made, although their records were not complete in this regard.

An attempt was made to correlate this decline with various factors such as food rationing, alcohol consumption, bread enrichment, nutrition education, and popular consumption of vitamin preparations. None of these seemed to have initiated the trend although some may have helped to perpetuate it. There was a good inverse correlation between the incidence of the disease and the general economic level of the population. It would seem a fair assumption that ability to purchase a more adequate diet was the principal factor initiating the virtual disappearance of this disease in their locality. One is reminded of the well established inverse relation between economic status and pellagra incidence in the South when pellagra was very common (J. Goldberger, G. A. Wheeler, E. Sydenstricker, and W. I. King, *U.S.P.H.S. Hygienic Lab. Bull. No.* **153,** *Jan. (1929)*).

The general incidence of pellagra in all parts of the United States has shown a similar but less spectacular decline. In many medical centers where pellagra was common, it is now difficult to find a single case for teaching purposes. This is reflected to some extent in a declining mortality rate as shown by figures from the Bureau of the Census. In 1930, 5.8 deaths per 100,000 population were reported as due to pellagra. In 1935 the rate was 2.8, in 1940, 1.6, and in 1946, 0.6. These lowered death rates undoubtedly reflect, in part, improved therapy and earlier recognition of the disease. However, the decline appeared to start about 1929, during a period of economic prosperity, nearly ten years before specific therapy was available. From 1932 to 1936 the death rate remained nearly constant at about 3.0 during the poor economic conditions of that time. As economic conditions began to improve, the rate again began to decline roughly paralleling the trend reported by Bean *et al.* (*loc. cit.*).

EFFECT OF ANTAGONISTS OF FOLIC ACID ON BLOOD FORMATION

Certain of the chemical analogues of pteroylglutamic acid have been shown to have an inhibitory effect on blood-forming tissues (*Nutrition Reviews* **6,** *23, 338 (1948)*). It is of importance that definitive description be achieved of the nature of the hematologic changes induced by this means.

V. Minnich and C. V. Moore (*Federation Proceedings* **7,** *276 (1948)*) studied the effects of large doses of 4-amino pteroylglutamic

acid (4-amino PGA) on guinea pigs. Daily subcutaneous injections of from 0.5 to 5.0 mg. of this antagonist were administered to animals on a stock ration. Varying degrees of hypoplasia of the bone marrow were observed. Changes in the peripheral blood included leukopenia in all, profound normocytic anemia in some, and agranulocytosis and thrombocytopenia in about 50 per cent of the animals. If administration of the antagonist was discontinued after these hematologic changes had become manifest, a few of the animals recovered, with reticulocytosis and recovery from depression in all of the cellular elements. Neither large doses of highly purified liver extract nor of folic acid provided protection against the quantities of 4-amino PGA administered.

Small quantities of 4-amino PGA and other analogues of folic acid have been administered to guinea pigs for longer periods in an attempt to assess the chronic hematologic effects of these materials (J. Innes, E. M. Innes, and C. V. Moore, *J. Lab. Clin. Med.* **34,** *883* (*1949*)). Adult guinea pigs were selected as animals for these experiments because they are intermediate in the spectrum of species susceptibility to these drugs and because of the similarity of cytology of peripheral blood and bone marrow of guinea pigs and of man.

The guinea pigs were provided a stock diet of lettuce and Purina rabbit chow. Antagonists were administered daily by injection. Before and during the period of administration of the drugs, frequent determinations were made of the red blood cell count, hemoglobin concentration, reticulocyte percentage, total and differential leucocyte counts, and platelet count. In addition, specimens of bone marrow aspirated from the ilium were examined at intervals.

Four analogues of pteroylglutamic acid were administered. Remarkably little hematologic effect was observed with daily injections for prolonged periods of pteroylaspartic acid-racemic form, pteroylaspartic acid-active form, or 7-methyl pteroic acid. In most instances there was continued mild reticulocytosis and in several animals given 7-methyl pteroic acid or the active form of pteroylaspartic acid there was persistent leucocytosis.

4-Amino PGA proved to be far more active hematologically than the three other folic acid antagonists. Daily administration of as little as 0.25 mg. of 4-amino PGA produced changes in the peripheral blood and in the bone marrow in from nine to thirteen weeks. When larger quantities were injected, changes occurred much earlier. Of greatest significance were the effects on the bone marrow. The marrow was of increased cellularity with many primitive erythrocytic and granulocytic cells and with reticulum cell hyperplasia. The bone marrow did not present the typical picture of pernicious anemia with megaloblastic arrest. In the peripheral blood there was evidence of depression of hematopoietic activity. There was anemia which was normochromic and normocytic in type. Leukopenia with diminution of lymphocytes as well as neutrophils was observed.

In several animals there was a decrease in the number of platelets and hemorrhage into tissues. Therefore, there were indications that each of the cellular elements of the blood was affected by 4-amino PGA. Withdrawal of this antagonist of folic acid after prolonged administration was followed within twenty-four hours by evidence of return to normal blood formation. Except in most extreme depression of hematopoiesis the effects of the drug were completely reversed when dosage was discontinued. These findings suggest that 4-amino PGA is excreted or metabolized rapidly and that its effects are contingent upon maintenance of a critical concentration in tissues. Although the two forms of pteroylaspartic acid and 7-methyl pteroic acid had little hematologic effect, each seemed to potentiate the action of small quantities of 4-amino PGA given simultaneously.

Experimental observations which demon-

strate an action of these materials resulting in depression of blood formation suggest their trial in patients with certain hematologic diseases. Adaptation has been made of 4-amino PGA and other analogues of folic acid for trial in the treatment of acute leukemia in man (S. Farber, *Blood* **4,** *160 (1949);* W. Dameshek, *Ibid.* **4,** *168 (1949)*). Although these drugs exhibit severe toxicity when administered to patients, temporary remissions of acute leukemia occur in a significant percentage of the patients receiving such therapy. It is not outside the realm of possibility that further investigations relative to these and other antagonists of folic acid may lead to important gains in the treatment of leukemia and other hematologic disorders.

HYPERTENSION RESULTING FROM A NUTRITIONAL DEFICIENCY

In the experimental animal, as well as in conditions met with in clinical experience, it is frequently true that a given symptom-complex may result from, or be modified by, several influences. Much has been written of the supposed ill effects of long-continued marginal deficiency states—both the impairment due to the deficiency *per se* as well as the influence of the submarginal state on the course of intercurrent diseases. Relatively little attention has been paid, however, to possible late effects of previously occurring acute deficiency disease.

The clinician has long recognized the occurrence of certain irreversible stages of deficiency diseases, such as permanent deformities of the bone resulting from rickets, incompletely reversible gastrointestinal changes in sprue, permanent fibrotic changes in cirrhosis of the liver, and the like. Even these, however, have not always received the attention they deserve.

A clear illustration of the potentialities inherent in the study of late effects of initial acute deficiencies is provided by the report of W. S. Hartroft and C. H. Best (*Brit. Med. J.* **1,** *423 (1949)*). These investigators placed weanling albino rats of the Wistar strain on a diet low in choline for periods of five or six days. Such brief periods of choline deficiency are sufficient for production of the typical "hemorrhagic kidney" in the young growing albino rat (*Nutrition Reviews* **1,** *156 (1943);* **2,** *314 (1944);* **4,** *345 (1946)*). In some of these experiments, the rats received the ration for four five-day intervals, separated by two-day periods during which the basal diet was supplemented with 0.35 per cent choline chloride. The animals were then transferred to a stock diet and observed for periods of from three to seven months. Control animals were pair-fed with those receiving the choline deficient diet—the controls received 0.35 per cent choline chloride throughout the time on the low choline basal diet.

Indirect blood pressure determinations were made at intervals during the experiment and terminal direct measurements were taken on each rat just before the animal was killed by bleeding. Blood pressure measurements and heart weights were recorded by an observer without knowledge of the group to which particular animals belonged. The data include observations on 62 rats surviving the acute renal hemorrhagic syndrome plus 36 control animals of similar age and weight. Upon termination of the experiment, histologic studies were made of both kidneys and the amount of renal damage observed was classified as severe, moderate, slight, or none.

Ten of the survivors of the hemorrhagic renal syndrome exhibited severe persistent kidney damage. All of these animals had definite arterial hypertension, the average blood pressure (systolic-diastolic mean) being 195 mm. of mercury and the heart weight averaged 0.55 per cent of the body weight in this group.

Thirteen of the survivors showed moderate residual renal damage. The mean blood pressure of this group was 165 mm. and the heart weight accounted for 0.37 per cent of body weight.

Thirty-nine of the survivors showed but slight renal damage. This group exhibited a mean blood pressure of 136 mm. and the cardiac weight represented 0.33 per cent of the total body weight.

For the 36 control animals, the mean blood pressure was 118 mm. of mercury, and the heart weight accounted for an average of 0.28 per cent of the total body weight. Only one of the controls exhibited an average blood pressure greater than 140 mm. of mercury. The correlation of hypertension, renal damage, and coronary enlargement is apparent.

The histologic picture of the damaged kidneys revealed destruction of the tubules with pronounced distention of other nephrons—many of these containing quantities of eosinophilic colloid. There was a definite reduction in the number of glomeruli and, in the severely damaged kidneys, thickening of the basement membranes throughout the capillary loops. The arterioles exhibited changes varying from early cellular proliferation of the media and adventitia to hyalinization and fibrinoid necrosis of the intima. Photomicrographs are presented in the paper illustrating these various changes.

The production of these permanent lesions requires comment. In groups of animals maintained on the choline deficient diet for seven to ten days, there was a very high mortality rate. When the small number of the survivors of this longer period of depletion were then given full diets for several months, no appreciable renal damage was seen at necropsy and no rise in blood pressure occurred. The longer period of choline deficiency would appear to result in the death during the acute stage of the most susceptible rats and allow the survival of only those animals in which renal damage did not occur. As would be expected, these less susceptible animals, then, did not exhibit the lasting renal changes and hypertension.

For production of the hypertensive syndrome, the authors emphasize the necessity of permitting growth to occur subsequent to the time of production of the acute renal lesions. They point out that failure to obtain their exact conditions probably accounts for the fact that other workers have failed to induce hypertension in rats following periods of choline deficient feeding.

The explanation of the probable mechanism of this experimental hypertension would seem to lie in the nature of the observed renal changes. It may be surmised that the pronounced reduction in glomerular capillary bed resulting from the deficiency of choline diminishes the renal blood flow. In fact, the authors liken these changes to the result of subtotal nephrectomy.

It is well known that any of several processes which bring about a diminution in the renal blood flow will produce peripheral vasoconstriction and hypertension mediated through a pressor substance formed in the ischemic kidney and poured into the blood stream (A. Blalock, *Physiol. Rev.* **20,** *159 (1940)*).

Hartroft and Best (*loc. cit.*) state that "When appreciable numbers of glomeruli are destroyed a train of events is apparently started leading to elevation of blood pressure. The hypertension in turn produces thickening of both the glomerular loops and arterioles." They further note that "There is no apparent immediate clinical application of these findings."

Despite the conservative view of these workers as to immediate clinical application of their findings, the studies are important because they provide another tool for production of experimental hypertension and, perhaps even more importantly, emphasize the need for "wider application of the principle of subjecting young animals to acute

deficiencies of one or more essential food factors, followed by periods of growth approaching or exceeding the normal in rate," in an effort to reveal hitherto unsuspected permanent effects of the initial acute deficiency.

PLASMA TOCOPHEROL LEVELS IN HEART DISEASE

There are at present no known clinical evidences of tocopherol deficiency in man. In searching for patients suffering from a lack of this vitamin, about the only criterion available is a therapeutic test. Such a procedure is subject to considerable uncertainty particularly when dealing with diseases which show spontaneous variations in intensity, and which may be amenable to subjective improvement through suggestion. Careful, controlled experiments and cautious, critical judgment are required in such situations. These factors are probably responsible for the many claims and denials which have appeared regarding the effectiveness of vitamin E in various cardiovascular diseases.

J. M. Lemley and associates (*Am. Heart J.* **37,** *1029 (1949)*) have approached this subject from a different direction which provides some badly needed objective data. They determined the plasma tocopherol levels in 21 healthy young adults, in 62 patients known to have cardiac disease, and in 42 individuals selected at random from the hospital wards. The young healthy adults showed an average of 1.09 ± 0.17 mg. per cent tocopherol in their plasma. This figure agreed well with data obtained by other investigators in similar subjects.

The 62 cardiac patients showed significantly lower plasma levels with an average value of 0.94 ± 0.35 mg. per cent. However, the random hospital ward group, which was comparable to the cardiac patients in age and sex, showed an average value of 0.92 ± 0.29 mg. per cent, again significantly lower than normal but not significantly different from the group with heart disease. When the frequency distribution of tocopherol levels was studied, some cardiac patients showed lower levels than did the normals but again this same characteristic was shown by the random ward group.

The patients with heart disease were further studied by dividing them into four classes according to the severity of their condition as recommended by the New York Heart Association ("Nomenclature and Criteria for Diagnosis of Diseases of the Heart," *Ed. 4, p. 71, J. J. Little & Ives Co., New York (1939)*). The plasma tocopherol levels of patients in each of the four cardiac classes were then compared. No significant differences were found.

Their data were also analyzed to see if there were consistent differences with respect to sex, color, or age. No correlation was found between tocopherol level and sex or color. There was a significant correlation between tocopherol level and age, the level rising with increasing age. The authors do not state the average ages of their various groups but it seems evident that the low tocopherol levels observed in the cardiac and ward groups cannot be explained on the basis of age.

If plasma tocopherol levels are a measure of tocopherol nutrition, the data in this study give no evidence for a direct relation between tocopherol nutrition and cardiac muscle function. It is possible that the plasma tocopherol level may bear no direct relation to the need for tocopherol in the tissues. It is also possible that the tissues may require increased amounts of this vitamin under certain conditions. By analogy to other vitamins one would expect the plasma tocopherol level to reflect, to some extent at least, the tocopherol concentration in the tissues, although this is not universally true with all vitamins.

One should also remember that some vita-

mins have actions when given in pharmacologic doses which are different from the reactions seen when the same vitamin is given in the correction of a deficiency state. Vitamin E might have a favorable effect on a disease even though the patient had a normal supply of this substance.

The data presented in this study offer no support for the use of vitamin E in treating coronary artery disease and other cardiovascular diseases as has been advocated by some. These latter reports have already been critically reviewed (*Nutrition Reviews* **5,** *164 (1947)*; **7,** *118, 278 (1949)*). Despite widespread publicity and public interest in the use of this vitamin for heart disease, this treatment has not been generally accepted in this country. The concensus seems to have been well expressed at a meeting of the American Medical Association, "Vitamin E is of no value in coronary artery disease, hypertension or rheumatic heart disease. The original claim that it is of benefit can be attributed to ceremonial therapy" (*J. Am. Med. Assn.* **136,** *810, 1031 (1948)*). The report of Lemley *et al.* (*loc. cit.*) would seem to strengthen this position.

NUTRITION OF ATHLETES

Considerable folklore has grown up extolling the peculiar virtue of one or another dietary regimen during athletic training or competition. That a sound basis does not exist for such folklore is well brought out in the published proceedings of a conference of the British Nutrition Society devoted to the subject (*Brit. J. Nutrition* **2,** *249 (1948)*). Participating in this symposium under the chairmanship of Professor J. R. Marrack were the following contributors: P. Eggleton, D. M. Needham, G. H. Bourne, C. A. Rumball, A. Abrahams, and R. N. A. Leyton. Subjects discussed ranged from fundamental considerations of the neuromuscular mechanism, chemistry of muscle contraction, tests for measurement of physical fitness, to questions of practical feeding of athletes.

The published proceedings make it clear that conclusive investigations are lacking on almost all points concerned with the nutrition of athletes. For example, it was pointed out that training allowances for calories have been estimated at some 7000 per day, a figure which seemed, on the basis of physiologic consideration, preposterously high. It was noted that athletes usually ingest large quantities of animal protein, especially meat. On the other hand, it was noted that certain champions are vegetarians; for example, Nurmi of Finland. Marrack summarized the discussion on these latter points as follows: "It seems that athletes eat meat because they like it and are debarred of many of the pleasures of life, and not for the sake of any special nutritive value of meat after absorption."

Discussion was made of the possible role of alterations in nutrition in promoting increased athletic abilities during the last fifty years as exemplified by the repeated breaking of one athletic record after another. It was opined that creation of new records could be satisfactorily explained by improvement in sports technic and by vastly increased competition and extension of athleticism throughout the world. Repeated expression was given to the view that too rigid dietary restriction and denial during training is a factor which may result in the psychologic handicap often termed "staleness."

In an effort to obtain some of the needed basic information as delineated by the above described conference, an investigation of Olympic athletes has been made (W. T. C. Berry *et al.*, *Brit. Med. J.* **1,** *300 (1949)*). These studies were completed while the ath-

letes were in London for the recent Olympic game. Participants of each nationality were housed together and ate either in a common dining room or, on occasions, in a central cafeteria. Food consumption studies were made on 28 subjects from nine nations. These individuals represented ages from 17 to 41 years, a variety of civil occupations, as well as participants in a number of different events. Food consumption study was over a four day period during which time duplicate meals were collected at each mealtime, and plate waste was saved for analysis and subtracted from the values of the duplicate meals. Chemical analyses were made for protein, fat, and carbohydrate. Calories were calculated by the factors 4, 9, 4 for protein, fat, and carbohydrate, respectively.

Protein consumption ranged from 65.0 to 231.0 g. per day with a mean of 139.0 g. These high intakes were due largely to meat, eggs, and milk. The range of dietary intake of fat was from 92.0 to 223.0 g. per day with an average of 137.0 g. Carbohydrate intakes varied from 128.0 to 572.0 g. per day, averaging 390.0 g. The caloric intake was not so high as has sometimes been estimated for athletes; it ranged from 2113 to 4739 daily with a mean daily consumption of 3350 calories. It was of interest that no consistent difference occurred between the different types of athletes. Estimations were also made of ascorbic acid consumption for 7 of the subjects; this varied from 41.0 to 98.0 mg. per day.

The estimated basal metabolism (it is not clear whether this was a determination or an estimate from height-weight-age data) plus 10 per cent of the calories supplied by the food (specific dynamic action) was subtracted from the intake to calculate the so-called "spare" calories. These "spare" calories available for activity ranged from 103 to 2303 per day or from approximately 1 to 31 "spare" calories per kilogram per day. Again, there was no consistent variation between numbers of "spare" calories consumed and type of event in which the athlete participated.

Twenty of the athletes were interviewed concerning their usual dietary habits, their food habits during training, and any alteration during competition. Most of them stated that they were constantly in training, and, hence, little change from their "normal" dietary habits occurred. The majority stressed the value of meat, eggs, and milk in the diet. Sugar, glucose, or salt were mentioned particularly by some of the athletes. Three of them made a point of taking a quantity of sugar in their drinks before a race, 2 took glucose each morning, 2 had glucose on the day of the race, 3 made a point of "plenty of salt in their food," and 2 took salt regularly when in strict training. Two runners took synthetic thiamine daily, and one jumper took preparations containing vitamins A, B, C, and D. Most of the athletes considered fat or fatty foods indigestible and avoided eating them in quantity before the event. There was no constancy in food practice on the day of the race.

Blood samples for hemoglobin determinations were obtained from 147 men, 16 to 47 years of age, representing eighteen countries. The mean hemoglobin level was 16.0 g. per 100 ml. with a standard deviation of 1.01 g.; the range was 13.7 to 18.6 g. Identical means were found for men from temperate and warmer tropical countries. No difference was demonstrated for the hemoglobin levels of men competing in various types of events. These observations on hemoglobin levels are particularly interesting inasmuch as they may be interpreted as representing values for man at his athletic optimal.

For a similar reason, the observations on blood pressure are worthy of note. Average values for 201 men were systolic, 119.1 mm. of mercury; diastolic, 77.4 mm. of mercury. Both systolic and diastolic pressures tended to increase with increasing body weight.

Additions to our knowledge of the nutrition of athletes should be welcomed by those

who have responsibility for their care and training and, in addition, should afford useful information on the nutritional level and physiologic attributes of that segment of our population which exhibits maximal physical fitness.

EFFECTS OF FLAVONES AND ASCORBIC ACID ON RADIATION SICKNESS

Excessive irradiation with roentgen rays or from radioactive materials produces the characteristic syndrome of radiation sickness. Manifestations of purpura frequently occur. Dietary factors have been demonstrated to be important in maintaining the integrity of vascular walls. Effects of certain food factors on the hemorrhagic diathesis of radiation sickness have been described (*Nutrition Reviews* **6,** *336* (*1948*)).

Among materials apparently influencing capillary permeability are flavones or the group of "vitamin P" substances (*Nutrition Reviews* **2,** *309* (*1944*)). It has been claimed that naturally occurring flavones protect animals against the effects of x-irradiation (J. Q. Griffith, E. Anthony, E. P. Pendergrass, and R. Perryman, *Proc. Soc. Exp. Biol. Med.* **64,** *332* (*1947*); P. E. Rekers and J. B. Field, *Science* **107,** *16* (*1948*)). This has been ascribed to protection afforded against capillary damage.

J. B. Field and P. E. Rekers (*J. Clin. Invest.* **28,** *746* (*1949*)) describe observations concerning the activity of flavones and related substances in irradiated dogs. The effects of these materials are compared with those of ascorbic acid, which has a role in the formation of the intercellular cement substance of the capillaries.

Dogs were maintained on a stated diet and received a standard single dose of x-irradiation delivered over the dorsal skin. The dosage given was 350 r, a quantity sufficient to produce death in approximately 50 per cent of the animals. Dogs in the test groups received 150 mg. daily of the flavones studied. The compounds were given orally in gelatin capsules incorporated in fresh ground beef. Administration of the test substances was begun one week prior to irradiation and continued for five weeks. Dogs in a control group received an amount of ground beef equivalent to that fed the test animals.

Of 37 untreated dogs given the standard dose of irradiation 64 per cent exhibited signs of hemorrhage and gross bleeding associated with leukopenia, anemia, and thrombocytopenia. Twenty-two dogs or 60 per cent of the group died within twenty days.

The effects of a number of flavonoid substances were tested. Included were the flavonol glucosides hesperidin, naringin, rutin, and quercitrin, the aglucone, quercitin, and derivatives, epimerized d-catechin, homoeriodictyol, hesperidin methyl chalcone, esculin, and morin. Each of these materials was given in the standard dosage and tested in groups of dogs varying in number from 5 to 10. In this dosage certain flavones seemed to have a beneficial effect on the course of radiation sickness whereas others were without demonstrable effect.

Treatment with hesperidin, epimerized d-catechin, homoeriodictyol, and morin reduced the incidence of hemorrhage and mortality of the irradiated dogs. Rutin, which was tested on a larger group of dogs, 27 in number, was associated with a reduction in mortality to 11 per cent and in gross bleeding to 22 per cent. Animals which succumbed to the effects of irradiation exhibited similar pathologic findings whether or not treated with flavones. There were hypoplasia of hematopoietic centers, generalized purpura, and visceral hemorrhage. Animals which survived exhibited fewer evidences of gross bleeding. Hematologic examinations demonstrated less anemia

and an increase in erythroblasts and nucleated red blood cells, as well as significantly lower erythrocyte sedimentation rates in dogs given flavones which reduced mortality rates and hemorrhage following irradiation. Those substances which were without effect on mortality rates and the incidence of purpura were likewise without effect on the hematologic manifestations of radiation sickness.

Twelve dogs given 300 mg. of ascorbic acid for one week prior to irradiation and for four weeks thereafter demonstrated no degree of protection from the standard dose of irradiation. The same quantity of ascorbic acid in combination with 150 mg. per day of hesperidin methyl chalcone or quercitin, two of the flavones previously determined to be inactive, was administered to other groups of dogs. Results of combination of ascorbic acid with hesperidin methyl chalcone were similar to those in control groups or in dogs given ascorbic acid alone. Mortality rate was reduced to 10 per cent when ascorbic acid was administered with quercitin, indicating the possibility of potentiation of activity between the two compounds.

In seeking an explanation for the protective effects of the flavones in radiation sickness, it was shown that the effect was not one upon the thrombocytopenia which accompanies the disease. The number of blood platelets is similarly reduced in untreated dogs, and in those receiving active flavones. Consideration was given to the possibility that increased hyaluronidase activity accompanies radiation sickness and is inhibited by flavones. Dopa and sodium gentisate, potent inhibitors of this enzyme, failed however to influence the course of the disease in dogs. The urinary excretion of hyaluronidase was unchanged in irradiation disease whether or not the animals were treated with rutin.

Observations recorded in these controlled experiments indicate important protection is provided by flavones in radiation sickness and that this is accomplished by counteraction of the harmful effect of irradiation on the integrity of the vascular wall. It is not surprising that there is variation in degree of activity with administration of compounds of related but varying structure. It would be of interest to have these observations extended to larger groups of animals and with variation in dosage to provide further comparison of degrees of activity. Demonstration of the mechanism of this action might provide significant information relative to the nature of radiation injury and the role of the flavones in body metabolism.

NOTES

Letter to the Editor

Dear Sir:

I am dissatisfied with the review "Neurologic Manifestations Associated with Vitamin A Deficiency in Young Ducks" (*Nutrition Reviews* **7,** *188 (1949)*).

The review of the paper by D. E. Fletcher and R. H. Rigdon (*Arch. Neurol. Psychiat.* **61,** *199 (1949)*) is essentially a short abstract of their paper. The concluding paragraph, for which *Nutrition Reviews* is responsible, expresses agreement with these authors that the effect of vitamin A deficiency on the nervous system is not entirely clear and that there seem to be important factors other than the disproportionate growth of skeleton and central nervous system which cannot be disregarded.

Specific mention is made of the paper by O. A. Bessey and myself ("Vitamin A Deficiency and the Nervous System," *Arch. Path.* **32,** *689 (1941)*). For this reason I think *Nutrition Reviews* should have presented to its readers the evidence we presented—that the mechanical factor resulting from retarded skeletal growth is a completely satisfactory explanation. The facts that we brought out, and which are essential for critical appraisal of the problem, may be summed up as follows: If vitamin A is directly essential for the growth of the central nervous system, pathologic results should be constant and should conform to a pattern of growth or an aspect of physiology manifested by a constant distribution of lesions. In the rat we found great irregularity in distribution and in degrees of involvement of the tracts in the spinal cord, and a complete lack of relationships of the tracts most commonly involved and the order of postnatal myelination. For example, in the individual rats "there were often marked differences in the two sides of the spinal cord; occasionally tracts which showed many degenerated fibers on one side would be practically free from lesions on the opposite side."

Another very important statement we made is that if the skeletal growth of young vitamin A deficient rats is retarded by an inadequate caloric intake, no nervous lesions occur, and the following statement appears in our paper: "The litter mates which received vitamin A with restriction of the quantity of food did not show signs of nerve lesions and on dissection the relations of nervous system to bone were within normal limits."

Finally, again we showed, and documented by illustrations, the fact that regenerative phenomena proximal to the constriction of nerve trunks gave proof "that the axons in vitamin A deficiency have undiminished powers of regeneration."

I think that your reviewer should have pointed out some of the inadequacies of the pathologic account by Fletcher and Rigdon. No mention is made of some very pertinent facts in regard to the anatomy of birds, particularly in the relationship of the central nervous system in regard to the enveloping skeletal structure. I read their paper very carefully when it appeared, and have re-read it and I would like to point out that the exact anatomic relationships of their gross findings in the spinal cord to the vertebral column are not given.

Inadequacies in description warrant challenging the statement in regard to the spinal cord—that it was enlarged as a result of "increasing volume of the grey and white substance." Can the authors possibly mean enlargement due to increase in numbers of neurons? I regard their evidence of bone formation in white and grey matter of the spinal cord as wholly unconvincing; their low-power photomicrographs are much more suggestive of artefact. As important a statement as they have made in regard to this

finding should have been thoroughly documented by an adequate description of the bone and cartilage found, particularly in relationship to the surrounding nervous tissue. In my own work with Dr. Bessey I found it extremely advantageous to fix the skeleton with nervous system *in situ*, and then both in undecalcified and in calcified preparations to remove the bone in order to see relationships *in situ*.

Excluding the presence of cartilage and bone in the spinal cord which can best be explained on the basis of artefact, an explanation supported by Fig. 2, p. 203 of their paper, and thoroughly warranted by absence of statements of histologic criteria necessary for consideration of an explanation based on the assumption of metaplasia of connective tissue within the spinal cord, all facts presented as questions to be answered (*Nutrition Reviews* **7,** *190 (1949)*), demand further elucidation.

The puzzles of the authors, in my opinion, would not have occurred had gross anatomic studies been made, adequate to establish accurately the relations of nervous tissues to the bony investment. They make no mention of the cervical enlargement of the vertebral canal, nor to the peculiar enlargement of the lumbosacral canal in the region of the sinus rhomboidalis. I looked in vain also for mention of the olfactory lobes in relation to the blood vessels, and of course for histologic bone studies which should have been made and described before launching the discussion on the absence of changes in the cerebrum, which is presented in the last paragraph of p. 208 of the authors' paper.

In the chick (S. B. Wolbach, *J. Bone Joint Surg.* **29,** *171 (1947)*), and therefore presumably in the duck, the effects of vitamin deficiency on skeletal growth are similar to those occurring in rats, guinea pigs, and dogs.

S. Burt Wolbach
Children's Hospital
Boston

Bulletin on Surveys

The National Research Council has issued Bulletin No. 117 entitled "Nutrition Surveys: Their Techniques and Value."

The Bulletin was prepared by a special committee of the Food and Nutrition Board under the chairmanship of Dr. C. G. King who states in his introduction to the Bulletin: "It is hoped that the present monograph will be useful in developing a better understanding of the value and purpose of nutrition surveys and that it will contribute to the development and use of improved techniques for conducting such studies."

The Bulletin is divided into seven sections as follows: The Objectives and Demonstrated Value of Nutrition Surveys; Dietary Surveys and Their Interpretation; Chemical Tests and Their Interpretation; Clinical Diagnosis in Nutrition Surveys; The Role of Surveys in Community Nutrition Programs; Nutrition Surveys in Relation to Professional Training in Schools of Medicine and Public Health; The Role of Health Departments in Nutrition Surveys and Appraisal.

Copies may be obtained from the National Research Council, 2101 Constitution Avenue, Washington 25, D. C. at a price of $1.50.

Recent Nutrition Books

The Scientific Feeding of Chickens. Ed. 2. Harry W. Titus. The Interstate Printers and Publishers, Inc., Danville, Ill. 1949. Pp. 253.

Annual Review of Biochemistry. Vol. XVIII. Edited by J. Murray Luck. Annual Reviews, Inc., Stanford, Calif. 1949. Pp. 739.

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